19365 Cp. 1801

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 10 July 1997 (10.07.97)	
International application No.: PCT/US96/20718	Applicant's or agent's file reference: P0985P2
International filing date: 19 December 1996 (19.12.96)	Priority date: 27 December 1995 (27.12.95)
Applicant: DE SAUVAGE, Frederic, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on: 16 June 1997 (16.06.97)

[ ] in a notice effecting later election filed with the International Bureau on: _____

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38

16I1

58/793,653

Copy for the Elected Office (EO/US) PCT/US96/20718

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

DREGER, Ginger, R.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
27 November 1997 (27.11.97)

Applicant's or agent's file reference
P0985P2

IMPORTANT NOTIFICATION

International application No.
PCT/US96/20718

International filing date (day/month/year)
19 December 1996 (19.12.96)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
GENENTECH, INC.
460 Point San Bruno Boulevard
South San Francisco, CA 94080
US

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990
US

State of Nationality: US
State of Residence: US
Telephone No.: (650)225-3216
Facsimile No.: (650)952-9881
Teleprinter No.:

3. Further observations, if necessary:
The change in address also applies to the agent.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
F. Gateau

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 001779277

16F1
08/793,453

Copy for the receiving Office (RO/US)

PCT/US96/20718

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

DREGER, Ginger, R.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
27 November 1997 (27.11.97)

Applicant's or agent's file reference
P0985P2

IMPORTANT NOTIFICATION

International application No.
PCT/US96/20718

International filing date (day/month/year)
19 December 1996 (19.12.96)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
GENENTECH, INC.
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South San Francisco, CA 94080
US

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990
US

State of Nationality: US
State of Residence: US
Telephone No.: (650)225-3216
Facsimile No.: (650)952-9881
Teleprinter No.:

3. Further observations, if necessary:
The change in address also applies to the agent.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
F. Gateau

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

001779277

793653
16x1

08/793653

PATENT COOPERATION TREATY

REC'D 30 MAR 1998
WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
SMK/FP5621289		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US96/20718	19/12/1996	27/12/1995
International Patent Classification (IPC) or national classification and IPC		
C12N15/16		
Applicant		
GENENTECH, INC.		

RECEIVED
MAY 21 1998

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/06/1997	23.03.98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Bilang, J Telephone No. (+49-89) 2399-8707

Form PCT/IPEA/409 (Cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US96/20718

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,3-30	as originally filed			
2	as received on	24/11/1997	with letter of	20/11/1997

Claims, No.:

1-26	as received on	24/11/1997	with letter of	20/11/1997

Drawings, sheets:

1/27-27/27	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 9-11, 23, and 24.

because:

☒ the said international application, or the said claims Nos. 9-11, 23, and 24 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8, 12-22, 25, 26
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Additional Remarks Item I

For the purpose of the present International Preliminary Examination Report the priority is assumed to be validly claimed. If the priority were not valid, the P-documents cited in the International Search Report would become relevant.

Additional remarks Item III

Claims 9-11, 23, and 24 concern methods for the treatment of the human or animal body. For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. In accordance with **Rule 67.1 (iv) PCT**, no opinion will therefore be given on the industrial applicability of said claims 9-11, 23, and 24.

Additional remarks Item V

The present application describes biologically active derivatives of the obese (OB) protein that have an increased half-life in the serum. In particular, the OB protein is fused to an immunoglobulin constant chain and/or to nonproteinaceous polymers like polyethylene glycol.

Immunoadhesins, i.e. chimeric antibody-like molecules that combine the functionnal domain of a binding protein (e.g. a ligand) with the immunoglobulin sequence, are well known in the art (paragraph bridging pages 8 and 9). However, the skilled person who has to develop a biologically active derivative of OB protein would not choose the solution provided by the present application. These derivatives are not necessarily expected to be able to cross the blood-brain barrier in order to reach the OB receptor.

Claims 1-26 are therefore deemed to involve an inventive step.

Additional remarks Item VI

The following documents could be relevant in the regional phase:

	publication date	filing date	priority date
WO 97/00319	03.01.1997	11.06.1996	13.06.1995
EP 0 741 187	06.11.1996	24.04.1996	05.05.1995
WO 96/05309	22.02.1996	17.08.1995	17.08.1994

Additional remarks Item VIII

1. The subject-matter of claims 1 and 2 is defined by the result which is to be achieved. According to **Rule 6.3(a) PCT**, the matter for which protection is sought should be defined in terms of the technical features of the invention.

2. It is not clear whether any covalent modification of an OB protein leads to a derivative having the desired properties. The addition of one or two amino acids to OB protein probably does not result in OB protein having a longer plasma half life than the native OB protein.

3. It is not clear how the OB protein is supposed to reduce the food intake of an individual (claim 1). It appears that what is meant is the biological function of OB protein of reducing the appetite. It is not clear whether a reduction in appetite in humans always leads to a reduced food intake.

4. Claim 4 covers a derivative of OB protein modified with a nonproteinaceous polymer. It is not clear whether any nonproteinaceous polymer is suitable to perform the invention. It must be suspected that e.g. PVC is not a suitable nonproteinaceous polymer.

expression of the *ob* gene in adipose tissue of mice with hypothalamic lesions does not result in a lean phenotype suggests that the OB protein does not act directly on fat cells. Maffei *et al.*, Proc. Natl. Acad. Sci. 92, 6957-60 (1995). Researchers suggest that at least one OB receptor is localized in the brain. The identification and expression cloning of a leptin receptor (OB-R) was reported by Tartaglia *et al.*, Cell 83, 1263-71 (1995). Various isoforms of a leptin receptor are described by Cioffi *et al.*, Nature Medicine 2, 585-89 (1996). A human hematopoetin receptor, which might be a receptor of the OB protein, is described in PCT application Publication No. WO 96/08510, published 21 March 1996. A receptor of the OB protein is disclosed in Tartaglia *et al.*, Cell 83, 1263-71 (1995).

Summary of the Invention

The present invention is based on the observation that the OB protein is significantly more effective at reducing body weight and adipose tissue weight when delivered as a continuous subcutaneous infusion than when the same dose is delivered as a daily subcutaneous injection. The invention is further based on the unexpected finding that a chimeric protein, in which the OB polypeptide is fused to an immunoglobulin constant domain, is strikingly more potent in reducing the body weight and adipose depots than native human OB, when both proteins are administered by subcutaneous injection once a day. The latter observation is particularly surprising since the OB protein-immunoglobulin chimera due to its large molecular weight, is not expected to be able to cross the blood-brain barrier, and reach the OB receptor which has been believed to be located in the brain.

In one aspect, the invention concerns long half-life derivatives of an OB protein capable of reducing body weight and/or food intake in an individual treated. The invention further concerns compositions containing such derivatives, and their administration for reducing body weight and/or food intake.

In another aspect, the invention concerns chimeric polypeptides comprising an OB protein amino acid sequence capable of binding to a native OB receptor linked to an immunoglobulin sequence (briefly referred to as OB-immunoglobulin chimeras or immunoadhesins). In a specific embodiment, the chimeric polypeptides comprise a fusion of an OB amino acid sequence capable of binding a native OB receptor, to an immunoglobulin constant domain sequence. The OB portion of the chimeras of the present invention preferably has sufficient amino acid sequences from a native OB protein to retain the ability to bind to and signal through a native OB receptor. Most preferably, the OB protein retains the ability to reduce body weight when administered to obese human or non-human subjects. The OB polypeptide is preferably human, and the fusion is preferably with an immunoglobulin heavy chain constant domain sequence. In a particular embodiment, the association of two OB polypeptide-immunoglobulin heavy chain fusions (e.g., via covalent linkage by disulfide bond(s)) results in a homodimeric immunoglobulin-like structure. An immunoglobulin light chain may further be associated with one or both of the OB-immunoglobulin chimeras in the disulfide-bonded dimer to yield a homotrimeric or homotetrameric structure.

The invention further concerns nucleic acid encoding chimeric polypeptide chains of the present invention, expression vectors containing DNA encoding such molecules, transformed host cells, and methods for the production of the molecules by cultivating transformant host cells.

CLAIMS

1. A covalent derivative of an OB protein having a longer plasma half-life and/or slower clearance than a corresponding native OB protein and capable of reducing body weight and/or food intake in an individual treated.

2. The derivative of claim 1 which is a derivative of a native human OB protein.

3. The derivative of claim 1 which is an OB-immunoglobulin chimera.

4. The derivative of claim 1 which is a native OB protein or an OB-immunoglobulin chimera modified with a nonproteinaceous polymer.

5. The derivative of claim 4 wherein the nonproteinaceous polymer is a polyethylene glycol (PEG).

6. A composition for the treatment of a condition associated with the abnormal expression or function of the OB gene, or for eliciting a biological response mediated by an OB receptor, comprising an effective amount of an OB derivative of claim 1.

7. The composition of claim 6 effective for weight and/or appetite reduction.

8. The composition of claim 6 effective in the reduction of elevated insulin levels.

9. A method for the treatment of a condition associated with the abnormal expression of function of the OB gene, or for eliciting a biological response mediated by an OB receptor, comprising administering to an individual to be treated as a derivative of claim 1.

10. The method of claim 9 wherein the condition to be treated is selected from the group consisting of obesity, bulemia, and Type I or II diabetes.

11. A method for inducing weight loss or appetite loss is a subject, comprising administering to said subject an effective amount of a derivative of claim 1.

12. A chimeric polypeptide comprising an OB protein amino acid sequence capable of binding to a native OB receptor, linked to an immunoglobulin sequence.

13. The chimeric polypeptide of claim 12 wherein said immunoglobulin sequence is a constant

domain sequence.

14. The chimeric polypeptide of claim 13 wherein said OB protein is human.

15. The chimeric polypeptide of claim 14 wherein two OB polypeptide-IgG heavy chain fusions are linked to each other by at least one disulfide bond to yield a homodimeric immunoglobulin-like structure.

16. The chimeric polypeptide of claim 15 wherein at least one of said OB polypeptide-IgG heavy chain fusions is associated with an immunoglobulin light chain.

17. An isolated nucleic acid sequence encoding an OB protein-immunoglobulin fusion.

18. A replicable expression vector comprising the nucleic acid of claim 17.

19. A host cell transformed with the replicable expression vector of claim 18.

20. A process comprising culturing the host cells of claim 19 so as to express the nucleic acid encoding an OB protein-immunoglobulin fusion.

21. The process of claim 20 wherein said host cells are cotransformed with nucleic acid encoding at least two OB protein-immunoglobulin fusions.

22. The process of claim 21 wherein said cells are further transformed with nucleic acid encoding at least one immunoglobulin light chain.

23. A method of treating a condition associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by an OB receptor comprising administering to a patient a therapeutically effective amount of the chimeric polypeptide of claim 12.

24. The method of claim 23 wherein said condition is selected from the group consisting of obesity, bulemia and type I or II diabetes.

25. A composition for the treatment of obesity comprising an effective amount of a chimeric polypeptide of claim 12 in association with a pharmaceutically acceptable carrier.

26. A method for inducing the growth of cells expressing an OB receptor comprising contacting said cells with the OB derivative of claim 1.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P0985P2		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 96/20718	19/12/1996	27/12/1995
Applicant		
GENENTECH, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   OB PROTEIN DERIVATIVES HAVING PROLONGED HALF LIFE.

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 20718

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-10,24-25
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-10, and 24-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/20718

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/16 C07K14/575 A61K38/22 C12N15/70 C12N1/21
//(C12N1/21,C12R1:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 00319 A (SMITHKLINE BEECHAM PLC ;BROWNE MICHAEL JOSEPH (GB); CHAPMAN CONRAD) 3 January 1997 see page 1, line 31 - line 33; claims; examples	1-4,7-26
P,X	EP 0 741 187 A (HOFFMANN LA ROCHE) 6 November 1996 see page 9, line 19 - page 11, line 46; claims; examples 19,20	1-3, 6-12,26
P,X	WO 96 05309 A (UNIV ROCKEFELLER ;FRIEDMAN JEFFREY M (US); ZHANG YIYING (US); PROE) 22 February 1996 see page 43, line 3 - page 46, line 14; claims	1-3, 6-12,26

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1997	14. 05. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Fuhr, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE, vol. 372, no. 6505, 1 December 1994, pages 425-432, XP000602062 YIYING ZHANG ET AL: "POSITIONAL CLONING OF THE MOUSE OBESE GENE AND ITS HUMAN HOMOLOGUE" see the whole document -----	1,10-12, 26

INTERNATIONAL SEARCH REPORT

:ernational application No.
PCT/US 96/ 20718

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-10, 24-25
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-10, and 24-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/20718

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9700319 A	03-01-97	AU 6011096 A	15-01-97
EP 0741187 A	06-11-96	AU 5197896 A	14-11-96
		CA 2175298 A	06-11-96
		ES 2093593 T	01-01-97
		JP 9003098 A	07-01-97
		NO 961796 A	06-11-96
		PL 314051 A	12-11-96
WO 9605309 A	22-02-96	AU 3329895 A	07-03-96
		CA 2195955 A	22-02-96
		DE 19531931 A	07-03-96
		FI 970656 A	17-02-97
		GB 2292382 A	21-02-96
		JP 9502729 T	18-03-97
		ZA 9506868 A	09-04-96